01997.044100.1 (NEW) PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: NEUHOLD et al.	)	Group Art Unit: 1632
Application No.: 09/717,450	)	Examiner: Wilson, Michael C.
Filed: November 20, 2000	)	Confirmation No.: 5417
For: TRANSGENIC ANIMAL MODEL FOR DEGENERATIVE DISEASES OF CARTILAGE	)	Customer No. 45743 (NEW)
	)	April 7, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Second Declaration of Dr. G. Roger Askew Under 37 C.F.R. §1.132

Sir:

1. I, G. Roger Askew, Ph.D., am a citizen of the United States of America, and am more than twenty-one years of age. I hereby declare as follows:

2 I presently hold the position of Associate Director, Molecular Genetics, Wyeth Research, Andover, Massachusetts, and have held this position for three years.

3. My qualifications as a scientist, and in particular in the field of transgenic animals and gene targeting, are set forth in my curriculum vitae, a copy of which is attached as Exhibit A.

4. The purpose of this declaration is to address the enablement-based and written description-based rejections of the claims currently pending and under consideration in U.S. Patent Application No. 09/717,450 (hereinafter "the '450 application"); these rejections are recited in the most recent United States Patent Office Communication, dated November 7, 2005 (hereinafter "the instant Office Action")

5. I have reviewed and am familiar with the instant Office Action, as well as the currently pending claims of the '450 application, which were submitted with the Response to Advisory Action and Request for Continued Examination, filed September 2, 2005.

6. In addition, I have re-reviewed and am familiar with my first Declaration, which was filed during prosecution of the '450 application on September 2, 2005. I have also reviewed and am familiar with the Second Declaration of Dr. Lisa A. Neuhold (hereinafter "the Second Neuhold Declaration"), which was originally filed during prosecution of U.S. Patent Application No. 08/994,689 on August 31, 2000, and filed during the prosecution of the '450 application on April 30, 2002. I am familiar with the art cited in the Second Neuhold Declaration at Tab 2 (i.e., Dietz and Sandell (1996) *J. Biol. Chem.* 271:3311-16 (hereinafter "Deitz") (Exhibit B) and Bosserhoff et al. (1997) *Dev. Dyn.* 208:516-25 (hereinafter "Bosserhoff") (Exhibit C)).

7. From reviewing the instant Office Action, it is my understanding that the Examiner believes that the phrase "chondrocyte-specific promoter," as recited in the

pending claims, is not adequately described in the '450 application for any promoter other than the type II collagen promoter. It is also my understanding that the Examiner believes that the '450 application does not enable one to make and use a transgenic rat commensurate with the scope of the claims due to the phrase "chondrocyte-specific promoter." This appears to be due to the Examiner's interpretation of the phrase "chondrocyte-specific promoter" to mean a promoter that produces a level of "expression in non-chondrocytes [that] is less than 10%" (the instant Office Action, at p. 11). The Examiner concludes that only the type II collagen promoter disclosed in the '450 application fits within the Examiner's definition of "chondrocyte-specific promoter"(id.).

8. Upon reading the specification, I believe that the Examiner has derived the 10% benchmark from the embodiment of "joint-specific expression" mentioned (as "typical") on page 15 of the '450 application, rather than relying on an art-established definition of "chondrocyte-specific promoter."

9. It is my belief that the phrase "chondrocyte-specific," in reference to the expression of genes and their promoters, has a well-established meaning to one of skill in the relevant art.

10. The phrase "chondrocyte-specific" is used in the field of bone, joint, and cartilage research to refer to a gene that is enriched in the chondrocytes of an organism relative to other cells of the organism. A gene enriched in the chondrocytes of an organism is said to be driven by a "chondrocyte-specific" promoter. The use of the term "specific" in

this context is as part of a term of art. In this term of art, or in similar terms of art, the term "specific" can have the same meaning as "selective." This interpretation is supported by the disclosure of the '450 application (see, e.g., page 6, lines 18-20, stating that "[s]elective expression ... results in regulated joint-specific expression"; and page 15, lines 20-21, stating "[j]oint-specific expression ... refers to expression that is greater in joints than in other cells").

11. It is further my opinion that many mouse and rat chondrocyte-specific genes, which are inherently driven by chondrocyte-specific promoters, were well known in the art at the time of filing the'450 application (November 20, 2000), and the parent application, U.S. Patent Application No. 08/994,689 (December 19, 1997).

12. I have reviewed a number of relevant research papers that provide examples of chondrocyte-specific genes, which are inherently driven by chondrocyte-specific promoters. It is clear from these papers that the phrase "chondrocyte-specific" is used to identify genes that are enriched in the chondrocytes of a particular organism. These finding are exemplified in the following references:

a. type II collagen (*col2a1*), which is disclosed in the '450 application, is referred to by Zhou et al. ((1995) *J. Cell. Sci.* 108:3677-84, 3677) (Exhibit D) as a "chondrocyte-specific" component of the cartilage extracellular matrix, even though *col2a1* is expressed in other tissues, such as eye, testes, epidermis, heart, and brain. In fact, Zhou et al. state that *col2a1* displays "chondrocyte-specific expression." (*Id.* at p. 3678);

b. the *CD-RAP* gene, which is discussed in the Second Neuhold Declaration, is described in Bosserhoff (Exhibit C), as a "gene specific to chondrogenesis [that] ... provides a template for study of chondrocyte-specific gene expression." (Bosserhoff at p. 520);

c. *collagens type II, IX* and *XI*, and *aggrecan*, which are expressed preferentially in chondrocytes, but are also expressed in tissues as diverse as bone, vitreous, heart and brain, are described as "chondrocyte-specific" by Goldring et al. ((1994) *J. Clin. Invest.* 94:2307-16, 2307) (Exhibit E); and

d. McDougall et al. ((1996) *J. Bone Min. Res.* 11:1130-38, 1130) (Exhibit F) describe *link* as a gene with "chondrocyte-specific" expression that have been known for many years, even though *link* is expressed in a variety of tissues, including ovary, ligaments, brain, eye, lung, stomach and kidney;

e. Bosnakovski et al. ((2006 Feb. 9) *Biotechnol. Bioeng.* [Epub ahead of print], Abstract) (Exhibit G) identify numerous genes that have been known for many years, e.g., *sox9*, *collagen type II*, *aggrecan*, and *cartilage oligomeric matrix protein* (*COMP*), as "chondrocyte-specific."

13. The promoters for at least the following genes that are known to be "chondrocyte-specific" have been isolated and characterized: mouse and rat *aggrecan* (Doege et al. (1994) *J. Biol. Chem.* 269:29232-40 (Exhibit H) and Watanabe et al. (1995) *Biochem. J.* 308:433-40 (Exhibit I)); mouse *CD-RAP* (Bosserhoff, *supra* (Exhibit C), Xie et al. (1998) *J. Biol. Chem.* 273:5026-32 (Exhibit J) and Xie et al. (2000) *Matrix Biology* 19:501-09 (Exhibit K)); mouse *collagen type IX* (Perala et al. (1994) *J. Biol. Chem.*

269:5064-71 (Exhibit L)); mouse *collagen type XI* (Tsumaki et al. (1996) *J. Cell Biol.* 134:1573-82 (Exhibit M)); mouse and rat *link protein* (Deak et al. (1999) *Cytogenet. Cell Genet.* 87:75-79 (Exhibit N) and Rhodes et al. (1991) *Nuc. Acids Res.* 19:1933-39 (Exhibit O)); mouse *COMP* (Issack et al. (2000) *J. Orthop. Res.* 18:345-50 (Exhibit P)); and mouse *Sox9* (Kanai and Koopman (1999) *Hum. Mol. Genet.* 8:691-96 (Exhibit Q)).

14. It is my opinion that the mouse and rat chondrocyte-specific promoters discussed above could be used to make a transgenic rat as set forth in the pending claims of the '450 application, and that one skilled in the art would immediately recognize that these "chondrocyte-specific" promoters could be used, along with the disclosure of the present invention, to produce a transgenic rat as claimed in the '450 application.

15. It is my opinion that one could isolate or synthesize the above-mentioned promoters by routine methods, such as polymerase chain reaction (PCR), restriction digest and cloning, or even chemical synthesis.

16. One such chondrocyte-specific promoter for use in a transgenic rat according to the claimed methods is the mouse *CD-RAP* promoter, as attested to by Dr. Neuhold in the Second Neuhold Declaration, and as disclosed in the references cited in the Second Neuhold Declaration, i.e., Bosserhoff (Exhibit C) and Dietz (Exhibit B).

17. Regardless of the appropriateness of an attempt to equate "joint-specific expression" with "chondrocyte-specific promoter," as the Examiner apparently attempts, and in addtion to my opinion regarding the above mentioned set of "chondrocyte-specific" genes and "chondrocyte-specific" promoters, it is my opinion that at least the *CD-RAP* promoter, as discussed in the papers cited in the Second Neuhold Declaration, would fit within the embodiment of "joint-specific expression" mentioned (as "typical") on page 15 of the '450 application (i.e., less than 10% expression in non-joint tissues), and relied on by the Examiner throughout the instant Office Action. For example, Deitz (Exhibit B) states at page 3315 that *CD-RAP* is found in "the cartilaginous tissues, but from none of the other tissues that were tested." It is my opinion, given the disclosure in Deitz (Exhibit B), that one skilled in the art would immediately recognize that the *CD-RAP* promoter is a "chondrocyte-specific promoter," and that one of skill in the art would immediately recognize that the *CD-RAP* promoter may be used, along with the disclosure of the present invention, to produce a transgenic rat according to the pending claims.

18. I further declare that all statements made herein are, to my knowledge, true, and that all such statements are based on information I believe to be true.

19. I further declare that these statements are made with the knowledge that willful false statements are punishable by fine or imprisonment or both, under Title 18, Section 1001, of the United States Code, and that such willful false statements may jeopardize the validity of the instant application and any patent issued thereupon.

Respectfully submitted,

April 7, 2006

Date

G. Roger Askew, Ph.D.

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